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Original Article

Sleep apnea and the subsequent risk of breast cancer in women: a nationwide population-based cohort study

Wei-Pin Chang [a], Mu-En Liu [b,c], Wei-Chiao Chang [d], Albert C. Yang [b,c], Yan-Chiou Ku [e], Jei-Tsung Pai [a], Yea-Wen Lin [a], Shih-Jen Tsai [b,c,*]

[a] Department of Healthcare Management, Yuanpei University, HsinChu, Taiwan
[b] Department of Psychiatry, Taipei Veterans General Hospital, Taipei, Taiwan
[c] Division of Psychiatry, School of Medicine, National Yang-Ming University, Taipei, Taiwan
[d] Department of Clinical Pharmacy, School of Pharmacy, Taipei Medical University, Taipei, Taiwan
[e] Nursing Department, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan

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ABSTRACT

Background: Hypoxia plays an important role in the development of solid tumors. Intermittent hypoxia is the hallmark of sleep apnea (SA). We tested the hypothesis that SA may increase the risk of breast cancer in Taiwan by using a population-based data set.
Methods: Our study cohort consisted of women diagnosed with SA between January 2003 and December 2005 ($n = 846$). For each SA patient, five age-matched control women were randomly selected as the comparison cohort ($n = 4230$). All participant cases were followed for 5 years from the index date to identify the development of breast cancer. Cox proportional-hazards regression was performed to evaluate the 5-year breast-cancer-free survival rates.
Results: Forty-four women developed breast cancer during the 5-year follow-up period, among whom 12 were SA patients and 32 were in the comparison cohort. The adjusted hazard ratio (HR) of breast cancer in patients with SA was higher [HR, 2.09; 95% confidence interval (CI), 1.06–4.12; $P < 0.05$] than that of the controls during the 5-year follow-up. Despite not meeting statistical significance, we found increases in the risk of breast cancer in women aged 30–59 years (HR, 2.06; 95% CI, 0.90–4.70) and ≥60 years (HR, 3.05; 95% CI, 0.90–10.32) compared with those aged 0–29 years.
Conclusion: The findings of our population-based study suggest an association between SA and an increased risk of breast cancer in women.

1. Introduction

Sleep apnea (SA) is a common sleep disorder characterized by multiple cessations of breathing during sleep that lead to intermittent hypoxia and sleep fragmentation. Each apnea, the period of the cessation of breathing, can last from 10 s to several minutes. The severity of SA is categorized as mild, moderate, or severe, based on the number of apneas per hour, and it is the most frequent medical cause of daytime sleepiness. Untreated SA has been shown to increase the risk of motor vehicle accidents [1], and evidence indicates that SA is a risk factor for diabetes and cardiovascular disease-related mortality and morbidity [2–6].

In a case report series, obstructive SA was present in patients with head and neck cancer at a prevalence of 76% (13/17), suggesting an association between obstructive SA and malignancies of the oral cavity and oropharynx [7]. In a cohort of 4910 suspected obstructive SA patients, Campos-Rodriguez et al. demonstrated that increased overnight hypoxia in severe SA was associated with an increased incidence of cancer [8]. Data from both animal and epidemiological studies also suggest a possible relationship between cancer progression and survival and the severity of SA [9–11].

The most common type of breast cancer originates in the milk ducts. Breast cancer occurs in both men and women, but is far more prevalent in women. Various seemingly unrelated factors have been shown to increase the risk of breast cancer. Hormone use, alcohol consumption, obesity, and nulliparity are each associated with a modest increase (<2-fold) in the risk of breast cancer. A family history of first-degree relatives with breast cancer is also associated with an increase (>2-fold) in the risk of breast cancer [12,13].

Hypoxia plays important roles in tumorigenesis, tumor angiogenesis, and metastasis [14]. Hypoxia leads to an adaptive re-

* Corresponding author at: Department of Psychiatry, Taipei Veterans General Hospital, No. 201, Shih-Pai Road, Sec. 2, 11217, Taipei, Taiwan. Tel.: +886 2 2875 7027 ext. 276; fax: +886 2 2872 5643.
E-mail address: tsai610913@gmail.com (S.-J. Tsai).

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sponse, orchestrated by hypoxia-inducible factor-1 (HIF-1), which is crucial for carcinogenesis and tumor progression [15]. Hypoxia is a microenvironmental selection force during somatic evolution in breast carcinogenesis. The level of HIF-1α is increased during carcinogenesis in breast tissue, and is associated with other tumor biomarkers, such as vascular endothelial growth factor [16]. Chen et al. recently demonstrated that the role of HIF-1α differs in the response, proliferation, and tumor progression phases of carcinogenesis in breast tissues [17].

Frequent, intermittent hypoxia in long-term SA may therefore lead to tumor carcinogenesis [18], thereby influencing the risk of breast cancer. However, evidence in support of this hypothesis is lacking, and no increased incidence of any type of cancer has been reported among women with long-term, frequent SA. Therefore, we examined the incidence of breast cancer during the first 5 years following a diagnosis of SA in a nationwide population-based cohort to determine the association between SA and subsequent breast cancer risk in women.

2. Methods

2.1. Database

The National Health Insurance Research Database (NHIRD) was established, and is managed, by the Taiwan National Health Research Institutes (NHRI). The NHIRD provides comprehensive health care data to researchers, including the enrollment files, claims data, catastrophic illness files, and various data regarding drug prescriptions. Our study data used the Longitudinal Health Insurance Database (LHID) 2005, a subset of the NHIRD. The LHID 2005 contains historical ambulatory data and inpatient care data for one million randomly sampled beneficiaries enrolled in the National Health Insurance (NHI) system between 1997 and 2010. The NHI provides comprehensive health care insurance for ~22.96 million residents of Taiwan. The NHRI has reported that there are no statistically significant differences in age or sex between the randomly sampled group and all beneficiaries of the NHI program. Because the NHI released the LHID 2005 database for research purposes, our study was exempt from full review by our institutional review boards.

2.2. Study population

The LHID 2005 was used to conduct a matched case-controlled study. A study cohort was compared with a control cohort to examine the relationship between SA and breast cancer in women. The study participants were linked to their claims data to identify the first diagnosis of SA based on the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes 327.23, 780.51, 780.53, and 780.57. For data accuracy, the included subjects were required to have received polysomnography and all ICD-9 codes were assigned by the otolaryngologist, pulmonologist, or neurologist. The date of the initial diagnosis of SA was assigned as the index date for each SA patient. Each SA cohort patient was matched based on age and index year to five randomly identified beneficiaries without SA to create the comparison cohort. Female patients diagnosed with breast cancer (ICD-9-CM code 174.X) before or after the study period were excluded from both cohorts. We also identified relevant comorbidities, including hypertension (ICD-9-CM 401.X-405.X), diabetes mellitus (ICD-9-CM 250.X), and hyperlipidemia (ICD-9-CM 272.X).

2.3. Level of urbanization

For our analysis of urbanization, all 365 townships in Taiwan were stratified into seven levels according to the standards established by the Taiwanese NHRI based on a cluster analysis of the 2000 Taiwan census data, with Level 1 referring to most urbanized and Level 7 referring to least urbanized. The criteria on which these strata were determined included the population density (persons/km^2), the number of physicians per 100,000 people, the percentage of people with a college education, the percentage of people aged >65 years, and the percentage of agricultural workers. Because levels 5, 6, and 7 contained few SA cases, they were combined into a single group, thereafter referred to as level 5.

2.4. Statistical analysis

Pearson χ^2-tests were performed to examine the differences in the categorical data between the SA and comparison cohorts, including the urbanization level, monthly income, region, and comorbidities. Survival analysis using the Kaplan–Meier method was also performed, and used the log-rank test to compare the survival distributions between the cohorts. The survival period was calculated for patients who suffered from SA until an occurrence of hospitalization, an ambulatory visit for breast cancer, or the end of the study period (December 31, 2010), whichever came first. After adjusting for monthly income, urbanization level, and the comorbidities as potential confounders, Cox proportional-hazards analysis stratified by age group and index year was performed to examine the risk of breast cancer during the 5-year follow-up in both cohorts. The age group factors in both groups were further classified. Stratified analysis was also performed regarding the underlying status of hypertension, diabetes, and hyperlipidemia to assess the association between SA and breast cancer events. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated to quantify the risk of breast cancer. Two-sided $P < 0.05$ was considered significant.

3. Results

Figure 1 shows the research design flowchart. The SA cohort contained 846 female patients, and 4230 female patients were included in the comparison cohort. The distributions of demographic characteristics and the comorbidities for the SA and comparison cohorts are shown in Table 1. Hypertension ($P < 0.001$), hyperlipidemia ($P < 0.001$), diabetes ($P < 0.001$), obesity ($P < 0.001$), alcohol use disorder ($P < 0.001$), and higher monthly income ($P = 0.002$) were more prevalent in the SA cohort than in the comparison cohort.

During the 5-year follow-up, 12 SA patients (1.4%) and 32 patients in the comparison cohort (0.8%) developed breast cancer. The

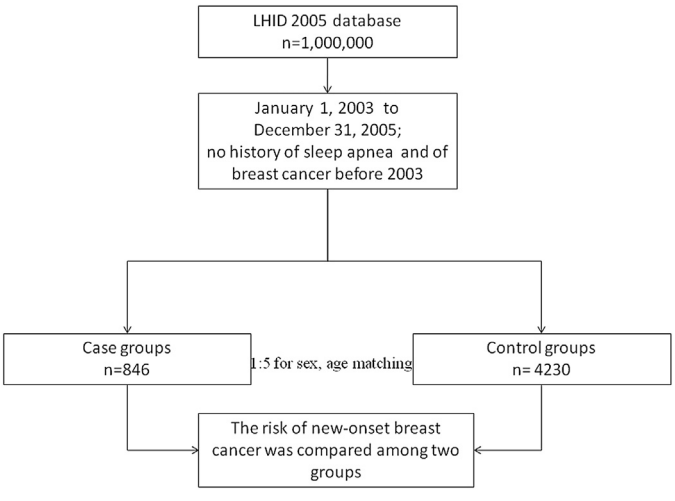

Fig. 1. Study research design. LHID, Longitudinal Health Insurance Database.

Table 1
Demographic characteristics for selected patients stratified by presence/absence of sleep apnea from 2003 to 2005 ($N = 5076$).

Characteristics	Sleep apnea cohort ($n = 846$)		Comparison cohort ($n = 4230$)		*P*-value
	n	%	*n*	%	
Age (years)					1
0–29	132	15.6	660	15.6	
30–59	512	60.5	2560	60.5	
≥60	202	23.9	1010	23.9	
Mean follow-up (years)	4.95	0.47	4.99	0.21	0.02
Urbanization level					0.005
1 (most urbanized)	307	36.3	1517	35.9	
2	263	31.1	1199	28.3	
3	137	16.2	588	13.9	
4	86	10.2	540	12.8	
5 (least urbanized)	53	6.3	386	9.1	
Monthly income (NT$)					0.002
0	229	27.1	1177	27.8	
1–15,840	128	15.1	450	10.6	
15,841–25,000	326	38.5	1797	42.5	
≥25,001	163	19.3	806	19.1	
Geographic region					0.001
North	378	44.7	2003	47.4	
Central	187	22.1	1061	25.1	
South	244	28.8	953	22.5	
Eastern	37	4.4	213	5.0	
Hypertension					<0.001
Yes	411	48.6	1550	36.6	
No	435	51.4	2680	63.4	
Hyperlipidemia					<0.001
Yes	378	44.7	1311	31.0	
No	468	55.3	2919	69.0	
Diabetes					<0.001
Yes	235	27.8	877	20.7	
No	611	72.2	3353	79.3	
Obesity					<0.001
Yes	55	6.5	97	2.3	
No	791	93.5	4133	97.7	
Alcohol use disorder					<0.001
Yes	10	1.2	7	0.2	
No	836	98.8	4223	99.8	

Kaplan–Meier survival curves are shown in Fig. 2. The curves demonstrated significantly lower breast-cancer-free survival rates in the SA cohort than in the comparison cohort (log-rank test, $P = 0.056$). The overall incidence density was higher in the SA cohort (2.87 per 1000 patient-years) than in the comparison cohort (1.52 per 1000 patient-years) (Table 2).

Cox regression analysis showed that the crude HR of breast cancer was 1.89 times greater for SA patients (95% CI, 0.97–3.67; $P = 0.06$) than for comparison patients. After adjusting for potential confounders, newly diagnosed SA was associated with an ~2.09 times greater risk of breast cancer (95% CI, 1.06–4.12; $P < 0.05$) compared with non-SA patients (Table 2). Although the stratified analysis did not reveal significant age-related differences in the risk of breast cancer, the adjusted HRs for patients aged 30–59 years (2.06) and patients ≥60 years of age (3.05) approached statistical significance (95% CI, 0.90–4.70 and 0.90–10.32, respectively) (Table 2).

4. Discussion

This is the first longitudinal study to use a large nationwide database to demonstrate an association between SA diagnosis and the developing breast cancer during the 5-year follow-up. The main finding of our study is that Cox proportional-hazards analysis stratified by age and index year yielded an adjusted HR of breast cancer that was 2.09 times greater for SA patients than for the comparison cohort. This result supports our hypotheses that SA may be a risk factor for developing breast cancer in women. Furthermore, our analysis showed that hypertension, hyperlipidemia, diabetes, stroke, and lower income were more prevalent in SA patients than in patients without SA, which is consistent with the results of previous studies [19,20], strengthening the reliability of our findings. However, whether our findings represent a causal relationship is unclear.

Several explanations should be considered. First, Campos-Rodriguez et al. demonstrated that increased overnight hypoxia was associated with increased cancer incidence [8]. Thus, intermittent hypoxia caused by SA may contribute directly to the risk of breast cancer. In vivo evidence has shown that hypoxia induces angiogenesis by upregulating connective tissue growth factor in human breast cancer cells [21]. Second, obesity is a risk factor for breast cancer [22], and is highly prevalent in SA patients [23,24]. An animal study found that both obesity and intermittent hypoxia are associated with increased tumor growth, but no synergistic effect was observed [25]. Thus, obesity among our SA patients may have contributed to the increase in the risk of breast cancer during the follow-up. However, the NHIRD does not contain information regarding obesity-related data, such as the body mass index, and we were unable to assess whether obesity was a potential confounding factor in this study. Further research is warranted to clarify the effect of obesity on the association between SA and breast cancer. Third, both SA and breast cancer involve complex interactions between genetic and environmental factors. Recent studies have shown that the apolipoprotein epsilon 4 (APOE4) allele is associated with an increased risk of SA [26]. Findings from previous studies regarding an association between APOE polymorphisms and breast cancer risk have, however, been inconsistent. A recent meta-analysis demonstrated an association of the APOE4 allele with an increased risk of breast cancer in an Asian population, and suggested that the APOE4 allele is a weak risk factor for the development of breast cancer [27]. These find-

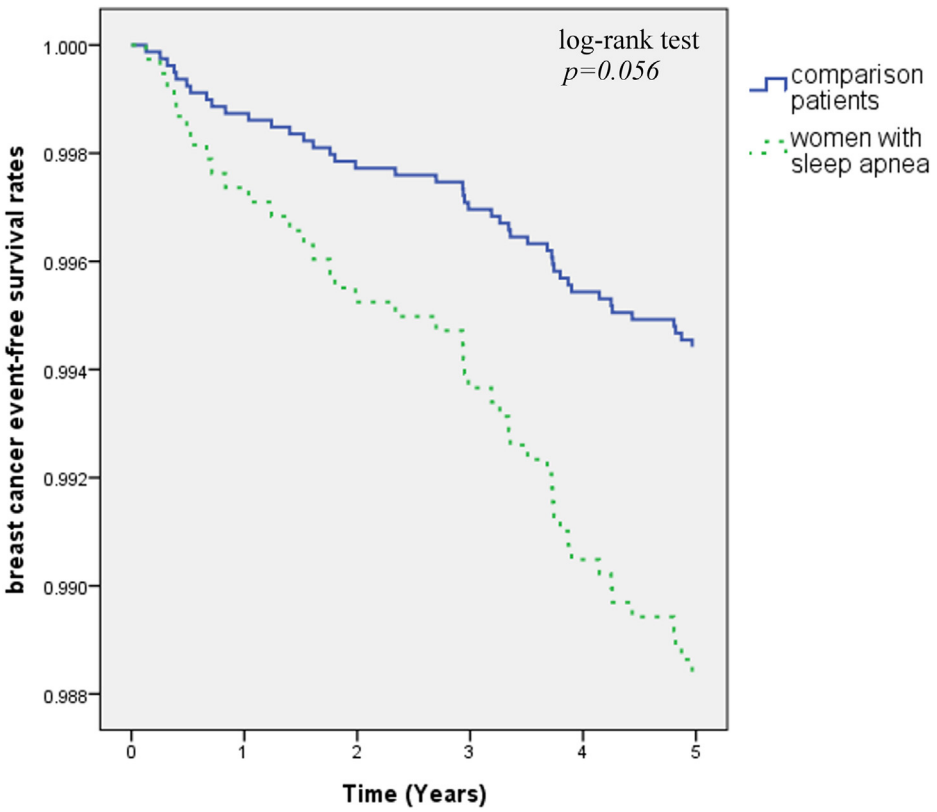

Fig. 2. Kaplan–Meier analysis of breast-cancer-free survival rates for patients with or without sleep apnea between 2003 and 2005.

ings suggest that SA and breast cancer may share a common genetic factor that may explain a higher prevalence of breast cancer among SA patients.

Studies on SA treatment have indicated that continuous positive airway pressure (CPAP) therapy can be effective in reducing SA nocturnal hypoxia and the associated comorbidity [28]. If overnight hypoxia in SA patients played a major role in the increased risk of breast cancer in the present study, then the findings suggest that CPAP therapy in SA patients may reduce their risk of breast cancer. Despite not meeting statistical significance, there were increases in the risk of breast cancer in patients aged 30–59 and ≥60 years compared with those aged 0–29 years. Indeed, the incidence of breast cancer rose with age, and significantly increased among women aged ≥50 years [29]. SA can enhance oxidative stress and inflammatory reaction [23], which are required for breast cancer malignant transformation and mammary gland carcinogenesis, and the normal mammary gland may be more vulnerable to those reactions with age [30]. Therefore, women aged >30 years may be more vulnerable to breast cancer development than those aged <30 years if they suffer from SA. The statistical power of our analysis may have been insufficient for the detection of a significant effect in our subgroups because of the small number of breast cancer cases that occurred during the 5-year follow-up. Future studies with longer follow-up periods or larger sample sizes are needed to confirm our findings regarding age-related effects on the risk of breast cancer.

One strength of the current study is the matched-control cohort study design, which considers many variables to minimize potential confounding factors. In addition, the NHI is a single-payer, mandatory health insurance program. The nationwide population-based data set of the NHIRD provided the large sample size and statistical power necessary to investigate an association between SA and the subsequent risk of breast cancer. The findings from our analysis of a nationwide population-based cohort provide support for an association between SA and breast cancer development in women.

Certain limitations to our findings should, however, be considered. First, study enrollment based on administrative claims data can be inaccurate, which is an inherent shortcoming in database research. In addition, most of the sleep centers in Taiwan follow the

Table 2
Overall and age-specific incidence densities and relative hazard of breast cancer in the sleep apnea and comparison cohorts.

Variable	Sleep apnea cohort				Comparison cohort				Crude HR	Adjusted HR[a]
	Incident cases	Person-years	ID[b]	95% CI	Incident cases	Person-years	ID[b]	95% CI		
Age (years)										
0–29	0	660.44	–	–	1	3298.52	0.30	−0.29–0.90	–	–
30–59	8	2526.54	3.17	0.98–5.36	23	12,766.57	1.80	1.07–2.54	1.76 (0.79–3.93)	2.06 (0.90–4.70)
≥60	4	999.59	4.00	0.09–7.92	8	5034.67	1.59	0.49–2.69	2.51 (0.76–8.35)	3.05 (0.90–10.32)
Total	12	4186.57	2.87	1.25–4.49	32	21,099.76	1.52	1.00–2.04	1.89 (0.97–3.67)	2.09 (1.06–4.12)*

Abbreviations: HR, hazard ratio; ID, incidence density (per 1000 patient-years); CI, confidence interval.
[a] Adjustments were made for age, monthly income, urbanization level, geographic region, hypertension, hyperlipidemia, diabetes, alcohol use disorder, and obesity.
[b] Based on Poisson assumption.
* $P < 0.05$.

guidelines of the American Academy of Sleep Medicine for the diagnosis of SA, which are based on both clinical and standard overnight polysomnographic assessments. Second, because NHIRD claims data are available only from 1997 onward, we could not determine the exact duration of SA for each patient. This in turn limited our ability to assess the interval between SA onset and incident breast cancer. Third, the NHIRD does not contain information regarding education, family history, tobacco use, body mass index, or alcohol consumption. Thus, we were unable to control for these potentially confounding factors. Fourth, the severity of SA and the treatment status for CPAP could not be determined based on the NHIRD claims data. Finally, severity of the SA, level of hypoxemia, and whether the patients with SA were treated for SA could not be determined from the registry. Future studies that consider these indices for the evaluation of the association between SA and breast cancer are warranted.

In conclusion, our study supports the hypothesis that SA may be associated with increased breast cancer risk in women. However, the specific mechanisms that underlie this association remain unknown, and further study is necessary to confirm our findings.

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Conflict of interest

None declared.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: http://dx.doi.org/10.1016/j.sleep.2014.05.026.

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References

[1] Philip P, Sagaspe P, Lagarde E, Leger D, Ohayon MM, Bioulac B, et al. Sleep disorders and accidental risk in a large group of regular registered highway drivers. Sleep Med 2010;11:973–9.
[2] Hale CS. Obstructive sleep apnea and cardiovascular disease and mortality: the argument for causality. J Insur Med 2005;37:272–82.
[3] Loke YK, Brown JW, Kwok CS, Niruban A, Myint PK. Association of obstructive sleep apnea with risk of serious cardiovascular events: a systematic review and meta-analysis. Circ Cardiovasc Qual Outcomes 2012;5:720–8.
[4] Pamidi S, Aronsohn RS, Tasali E. Obstructive sleep apnea: role in the risk and severity of diabetes. Best Pract Res Clin Endocrinol Metab 2010;24:703–15.
[5] Parati G, Lombardi C, Narkiewicz K. Sleep apnea: epidemiology, pathophysiology, and relation to cardiovascular risk. Am J Physiol Regul Integr Comp Physiol 2007;293:R1671–83.
[6] Johansson P, Alehagen U, Ulander M, Svanborg E, Dahlstrom U, Brostrom A. Sleep disordered breathing in community dwelling elderly: associations with cardiovascular disease, impaired systolic function, and mortality after a six-year follow-up. Sleep Med 2011;12:748–53.
[7] Payne RJ, Hier MP, Kost KM, Black MJ, Zeitouni AG, Frenkiel S, et al. High prevalence of obstructive sleep apnea among patients with head and neck cancer. J Otolaryngol 2005;34:304–11.
[8] Campos-Rodriguez F, Martinez-Garcia MA, Martinez M, Duran-Cantolla J, Pena Mde L, Masdeu MJ, et al. Association between obstructive sleep apnea and cancer incidence in a large multicenter Spanish cohort. Am J Respir Crit Care Med 2013;187:99–105.
[9] Almendros I, Montserrat JM, Ramirez J, Torres M, Duran-Cantolla J, Navajas D, et al. Intermittent hypoxia enhances cancer progression in a mouse model of sleep apnoea. Eur Respir J 2012;39:215–17.
[10] Campos-Rodriguez F, Pena-Grinan N, Reyes-Nunez N, De la Cruz-Moron I, Perez-Ronchel J, De la Vega-Gallardo F, et al. Mortality in obstructive sleep apnea–hypopnea patients treated with positive airway pressure. Chest 2005;128:624–33.
[11] Young T, Finn L, Peppard PE, Szklo-Coxe M, Austin D, Nieto FJ, et al. Sleep disordered breathing and mortality: eighteen-year follow-up of the Wisconsin sleep cohort. Sleep 2008;31:1071–8.
[12] Nelson HD, Zakher B, Cantor A, Fu R, Griffin J, O'Meara ES, et al. Risk factors for breast cancer for women aged 40 to 49 years: a systematic review and meta-analysis. Ann Intern Med 2012;156:635–48.
[13] Singletary SE. Rating the risk factors for breast cancer. Ann Surg 2003;237:474–82.
[14] Wouters BG, Koritzinsky M. Hypoxia signalling through mTOR and the unfolded protein response in cancer. Nat Rev Cancer 2008;8:851–64.
[15] Milani M, Harris AL. Targeting tumour hypoxia in breast cancer. Eur J Cancer 2008;44:2766–73.
[16] Bos R, Zhong H, Hanrahan CF, Mommers EC, Semenza GL, Pinedo HM, et al. Levels of hypoxia-inducible factor-1 alpha during breast carcinogenesis. J Natl Cancer Inst 2001;93:309–14.
[17] Chen CL, Chu JS, Su WC, Huang SC, Lee WY. Hypoxia and metabolic phenotypes during breast carcinogenesis: expression of HIF-1alpha, GLUT1, and CAIX. Virchows Arch 2010;457:53–61.
[18] Abrams B. Cancer and sleep apnea – the hypoxia connection. Med Hypotheses 2007;68:232.
[19] Lee W, Nagubadi S, Kryger MH, Mokhlesi B. Epidemiology of obstructive sleep apnea: a population-based perspective. Expert Rev Respir Med 2008;2:349–64.
[20] Mansukhani MP, Calvin AD, Kolla BP, Brown RD Jr, Lipford MC, Somers VK, et al. The association between atrial fibrillation and stroke in patients with obstructive sleep apnea: a population-based case–control study. Sleep Med 2013;14:243–6.
[21] Shimo T, Kubota S, Kondo S, Nakanishi T, Sasaki A, Mese H, et al. Connective tissue growth factor as a major angiogenic agent that is induced by hypoxia in a human breast cancer cell line. Cancer Lett 2001;174:57–64.
[22] Anderson GL, Neuhouser ML. Obesity and the risk for premenopausal and postmenopausal breast cancer. Cancer Prev Res (Phila) 2012;5:515–21.
[23] Mehra R, Redline S. Sleep apnea: a proinflammatory disorder that coaggregates with obesity. J Allergy Clin Immunol 2008;121:1096–102.
[24] Fulop T, Hickson DA, Wyatt SB, Bhagat R, Rack M, Gowdy O Jr, et al. Sleep-disordered breathing symptoms among African-Americans in the Jackson Heart Study. Sleep Med 2012;13:1039–49.
[25] Almendros I, Montserrat JM, Torres M, Bonsignore MR, Chimenti L, Navajas D, et al. Obesity and intermittent hypoxia increase tumor growth in a mouse model of sleep apnea. Sleep Med 2012;13:1254–60.
[26] O'Hara R, Luzon A, Hubbard J, Zeitzer JM. Sleep apnea, apolipoprotein epsilon 4 allele, and TBI: mechanism for cognitive dysfunction and development of dementia. J Rehabil Res Dev 2009;46:837–50.
[27] Saadat M. Apolipoprotein E (APOE) polymorphisms and susceptibility to breast cancer: a meta-analysis. Cancer Res Treat 2012;44:121–6.
[28] Yamamoto H, Teramoto S, Yamaguchi Y, Ouchi Y. Effect of nasal continuous positive airway pressure treatment on plasma adrenomedullin levels in patients with obstructive sleep apnea syndrome: roles of nocturnal hypoxia and oxidant stress. Hypertens Res 2007;30:1065–76.
[29] Hirko KA, Soliman AS, Hablas A, Seifeldin IA, Ramadan M, Banerjee M, et al. Trends in breast cancer incidence rates by age and stage at diagnosis in Gharbiah, Egypt, over 10 years (1999–2008). J Cancer Epidemiol 2013;2013:916394.
[30] Bonafe M, Storci G, Franceschi C. Inflamm-aging of the stem cell niche: breast cancer as a paradigmatic example: breakdown of the multi-shell cytokine network fuels cancer in aged people. Bioessays 2012;34:40–9.